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Osteoimmunology: memorandum for rheumatologists

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Rapid progress has been made in exploring the connections between the skeletal system and the immune system over the past decade. Bone tissue forms developmental niches for hematopoietic stem cells, and activated immune cells are involved in bone metabolism regulation and are potent mediators of osteoporosis and bone erosion under pathological conditions. The interdisciplinary field of osteoimmunology has emerged to pool the knowledge of the interdependence of these two systems, including the shared ligands and receptors, their crosstalk and interaction, and common intracellular signaling pathways with bidirectional influence. The receptor activator of nuclear factor-kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) triad is the key vinculum, with multifaceted potency, being not only essential for osteoclastogenesis but also critical for lymph node organogenesis and lymphopoiesis as well as for immune regulation. In this review, we summarize the progress in this area, focusing on those aspects of interest concerning rheumatic diseases.

osteoimmunology, bone remodeling, osteoclastogenesis, immune cells, RANKL

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INTRODUCTION

Bone is a biologically dynamic entity with permanent cell activity and continuous remodeling, rather than a static, unchanging tissue. Weight bearing, hematogenesis and coordination of calcium homeostasis are the primary roles of bone tissue. However, immune regulation and immunogenesis are also key roles of bone according to updated knowledge about the codependence of the immune system and the skeletal system, as elucidated by osteoimmunology. Osteoblasts (OBs) originate from mesenchymal stem cells (MSC) and contribute to bone resorption, whereas osteoclasts (OCs) originate from hematopoietic precursors belonging to monocyte and macrophage lineages and are responsible for bone formation. Concerted bone synthesis and bone degradation mediate bone turnover, also known as bone remodeling, which helps to maintain bone density and bone architecture. Bone remodeling starts from the embryonic development period and continues throughout the whole lifespan, which is the fundamental adaptive mechanism of bone in coping with biomechanical pressure and bone damage repair. If the dynamic balance of bone remodeling is skewed toward activated bone resorption, bone loss via either osteoporosis (OP) or bone erosion will occur, as observed in rheumatoid arthritis (RA) and other diseases with systemic inflammatory bone loss.

The term "osteoimmunology" was first introduced by Joseph R. Arron and Yongwon Choi in 2000 (Arron and Choi, 2000). This new discipline has helped to demonstrate the concept that the skeletal system and immune system have an intense interaction and should be considered as a functional unit. Ever since 2000, cumulative evidence of the interplay between immune cells and bone metabolism has

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been obtained, and clinically relevant diseases, such as RA, spondyloarthropathy (SPA), postmenopausal OP, and periodontal disease (PD), have been investigated. This review will summarize current understanding in this field and concentrate on those aspects that interest rheumatologists.

BONE METABOLISM

OBs, OCs and osteocytes collaborate in continuous bone remodeling and bone mass renewal. OCs are specifically tartrate-resistant acid phosphatase (TRAP)-positive, multinucleated giant cells with polarized ruffled borders that are involved in bone absorption. Cathepsin K, integrin β3, the calcitonin receptor and matrix metalloprotein 9 (MMP9) are the primary markers of OCs (Greisen et al., 2015), and nuclear factor of activated T-cells 1 (NFATc1) and c-Fos are the essential transcription factors for osteoclastogenesis (Takayanagi, 2005, 2007; Wagner and Eferl, 2005). In contrast, OBs are basophilic, mononuclear polygonal cells that contribute to bone matrix synthesis by secreting osteoid, embedding themselves into the matrix and then transforming into osteocytes during mineralization, thus contributing to new bone formation. Runt-related transcription factor 2 (Runx2) and peroxisome proliferator-activated receptor gamma (PPARγ) are the specific transcription factors involved in osteoblastogenesis (Komori, 2011). The bone morphogenetic protein (BMP) cascade and Wnt/β-catenin signaling are other central players in osteoblastogenesis through stimulation of Runx2, thus contributing to establishing and maintaining peak bone mass (Baron et al., 2006) (Figure 1).

During the physiological bone remodeling process, OCs

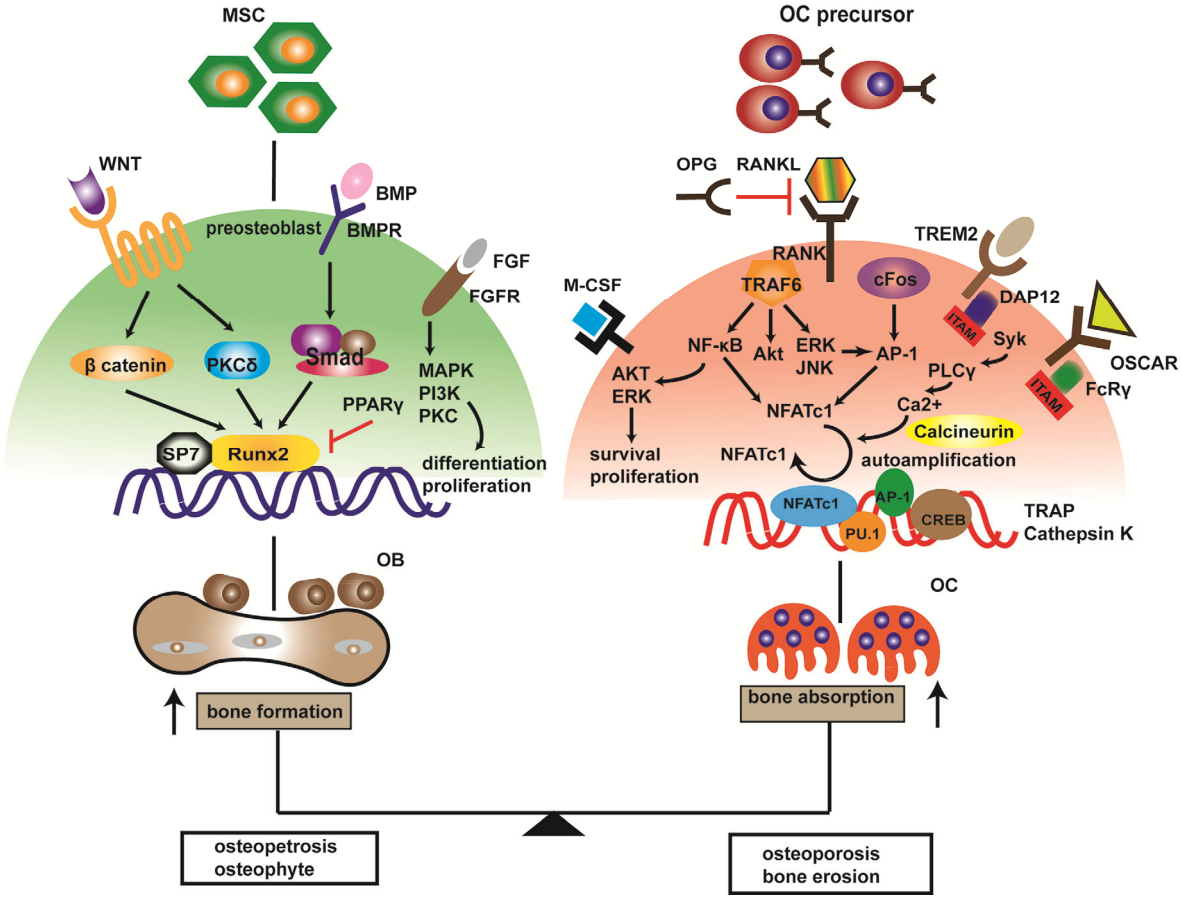

Figure 1 Critical signaling molecules and transcription factors in osteoblastogenesis and osteoclastogenesis. OBs derive from mesenchymal stem cells (MSC) and function as bone formation cells. BMP and Wnt/β-catenin are the main signaling pathways contributing to osteoblastogenesis, and Runx2 is the main transcription factors needed for OB differentiation and maturation and is antagonized by PPARγ. Meanwhile, OCs belong to the monocyte and macrophage lineages and function as bone absorption cells, and the RANK-RANKL axis is the central signaling pathway in osteoclastogenesis. TREM2-DAP12 and OSCAR-FcγR associated with intracellular ITAMs are also involved. The downstream adaptor protein TRAF6 stimulates NFATc1, which is the main transcription factor for osteoclastogenic gene activation. Broken equilibrium of bone formation and bone absorption will lead to pathological bone remodeling. FGF, fibroblast growth factor; BMP, bone morphogenetic protein; BMPR, BMP receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; ERK, extracellular regulated kinase; JNK, JUN N-terminal kinase; ITAM, immunoreceptor tyrosine-based activation motif; OSCAR, osteoclast-associated receptor; TREM2, triggering receptor expressed on myeloid cells-2; DAP12, DNAX-activating protein 12; RANK, receptor activator of nuclear factor-kappa B; RANKL, RANK ligand; OPG, osteoprotegerin; TRAF6, tumor necrosis factor receptor-associated factor 6; NFATc1, nuclear factor of activated T-cells 1; PPARγ, peroxisome proliferator-activated receptor gamma.

and OBs are sequentially recruited and activated. Bone resorption is followed by bone formation, composing a coupling of activities that is delicately regulated. Broken equilibrium of the OBs' and OCs' activities leads to abnormal bone remodeling, with increased or decreased bone mass (osteopetrosis or OP, respectively). Several hormones, such as estrogen, parathyroid hormone (PTH), calcitonin and vitamin D3, are involved in bone remodeling. Estrogen exhibits bone-protective effects, as revealed by the occurrence of OP after menopause as well as by disease alleviation during pregnancy and aggravation after delivery in RA patients, which parallel the waxing and waning of estrogen levels. In contrast, the role of PTH in regulating bone remodeling is much more complicated and double edged, with both anabolic and catabolic effects. Intermittent administration of PTH may stimulate OB differentiation and inhibit OB apoptosis, thus promoting bone formation. Based on this anabolic effect of PTH, the FDA has approved it for OP treatment. However, continuous injection of PTH is reported to facilitate OC formation and to promote bone absorption (Qin et al., 2004). Meanwhile, calcitonin targets activated OCs and inhibits bone resorption, resulting in decreased serum calcium levels and increased bone mineral density (Karsdal et al., 2008). Finally, treatment with vitamin D3 is beneficial for bone biology by increasing bone mineralization and promoting OB differentiation *in vivo*, in contrast to its pro-osteoclastogenic effects *in vitro* (Yoshida and Stern, 2012).

STRUCTURAL AND ANATOMIC CONNECTIONS BETWEEN BONE CELLS AND IMMUNE CELLS

Cortical bone and cancellous bone constitute the entity of bone tissue. The bone marrow space is loosely compartmentalized and accommodates hematopoietic precursors and trabecular bone. Bone cells and hematopoietic cells share this same microenvironment, with the bone marrow providing a milieu that allows bone cells and hematopoietic precursors to come into close contact and to influence each other. Hematopoietic precursors scatter around the trabecular bone, forming a hematopoietic focus from which immune cells derive. The bone marrow is also the reservoir where memory T/B cells are homing to and where these cells survive for a long time after leaving the secondary lymphoid organs. The nutritive periosteal vasculature provides additional anatomic bases for further communication between the two systems. These vessels penetrate cortical bone, carrying circulatory pro-inflammatory components and assisting OC precursors homing from the synovium to bone. Endothelial cells and MSC, mature OBs and OCs, osteolineage-derived proteins (e.g., annexin II, angiopoietin I) and cytokines (e.g., interleukin (IL)-10, stem cell factor) participate in constructing the hematopoietic stem cell (HSC) niche, which is a hematopoietic microenvironment that supports survival and self-renewal of HSCs and controls the fate of immune cells (Calvi et al., 2003; Zhang et al., 2003). OBs are thought to be a regulatory component of HSC niches that contribute to hematopoietic progenitor growth and HSC pool maintenance through Notch activation and osteopontin (OPN) secretion (Calvi et al., 2003; Nilsson et al., 2005). CXC chemokine ligand 12 (CXCL12)-abundant reticular cells have the potential to differentiate into OBs in mice and are involved in the endosteal niches that regulate HSC maintenance (Sugiyama and Nagasawa, 2012). Annexin-deficient mice have decreased HSC numbers and impaired localization of HSCs to endosteal niches (Jung et al., 2007; Jung et al., 2011). In contrast, the role of OCs in regulating the mobilization of hematopoietic progenitors and modifying HSC niches is controversial. It has been reported that OCs release proteolytic enzymes (e.g., MMP9) to degrade endosteal components and to promote hematopoietic progenitor mobilization into the circulation (Kollet et al., 2006). However, the mobilization of HSCs induced by serial granulocyte colony-stimulating factor (G-CSF) injection is normal in osteopetrotic mice lacking OCs, indicating that OCs are not indispensable for HSC maintenance and mobilization, as previously thought (Miyamoto et al., 2011).

RECIPROCAL INTERACTION BETWEEN IMMUNE SYSTEM AND SKELETAL SYSTEM IMPLICATED FROM ANIMAL MODELS

Many transcription factors and molecules are shared by the skeletal system and immune system. Genetically modified animal models shed light on the bidirectional influence of these mediators. In mouse models, compromised immune cell development and responses coexist with disturbed bone remodeling (Table 1).

The Pax5 gene encodes B cell lineage-specific activator protein (BSAP), a transcription factor involved in B cell lineage commitment and development below the proB stage (Nutt et al., 1999). $Pax5^{-/-}$ mice display arrested B cell development beyond the proB stage, with severe bone loss and increased OC numbers (Horowitz et al., 2004). $Pax5^{-/-}$ proB cells lose their B lineage commitment, while owning multilineage potential. Under proper stimulation, $Pax5^{-/-}$ proB cells can be induced to differentiate into OCs (Nutt et al., 1999). PU.1 is another transcription factor and is required for the development of both the B lineage and the myeloid lineage (McKercher et al., 1999). PU.1 knockout mice exhibit osteopetrosis, along with absence of OCs and macrophages as well as deficiency of B cells, indicating the participation of PU.1 in both osteoclastogenesis and B lymphopoiesis (McKercher et al., 1996; Tondravi et al., 1997). B cell lymphoma 6 (Bcl-6) is required by germinal center B cells to escape from the fate of apoptosis induced by DNA damage; to maintain self-renewal and survival; and to allow

Table 1 Genetically modified animal models displaying a reciprocal interaction between immune cells and bone remodeling[a)]

Mouse model	Function of the modified gene/molecule	Bone remodeling phenotype	Influence on immune cells and HSCs	Reference
RANK-Tg	RANK: binds with RANKL, activates NF-κB via intracellular signaling cascade transduction and induces OC differentiation and maturation	Osteoporosis	Enlarged cutaneous lymph nodes	(Hess et al., 2012)
RANK$^{-/-}$	Same as above	Osteopetrosis; tooth loss	B cell deficiency and abnormal B com partment; lack of peripheral lymph nodes	(Dougall et al., 1999; Marrella et al., 2015)
RANKL-Tg	RANKL: binds to RANK and stimulates OC formation	Osteoporosis	Increased mTEC cells and enlarged thymic medulla	(Ohigashi et al., 2011)
RANKL$^{-/-}$	Same as above	Osteopetrosis; tooth loss	Defective differentiation of early T/B lymphocytes; lack of peripheral lymph nodes; shrinking thymus	(Kong et al., 1999b)
OPG-Tg	OPG: decoy receptor for RANKL; prevents RANKL-induced bone absorption and induces monocytes chemotaxis and adhesion	Osteopetrosis	Extramedullary hematopoiesis	(Simonet et al., 1997; Stolina et al., 2007)
OPG$^{-/-}$	Same as above	Osteoporosis	Induction of monocyte chemotaxis and promotion of monocyte adhesion	(Bucay et al., 1998; Mizuno et al., 1998)
c-Fos$^{-/-}$	c-Fos: component of activator protein 1; essential for OC differentiation	Osteopetrosis	Reduced B cell number in the spleen and increased $CD4^+$ or $CD8^+$ thymocyte number but reduced number of double-positive T cells	(Okada et al., 1994; Wang et al., 1992)
TRAF6$^{-/-}$	TRAF6: intracellular adaptor protein	Osteopetrosis; Tooth eruption	Impaired response to LPS; impaired B cell proliferation in response to CD40 and LPS induction	(Lomaga et al., 1999)
Pax5$^{-/-}$	Pax5: helps to maintain B lineage commitment and regulates transition from proB to preB	Osteopenia	ProB accumulation; lack of following stage of B cells	(Horowitz et al., 2004; Nutt et al., 1999)
PU.1$^{-/-}$	PU.1: involved in B cell and myeloid lineage development	Osteopetrosis	Absence of B cells and macrophages	(McKercher et al., 1996; Tondravi et al., 1997)
Bcl-6$^{-/-}$	Bcl-6: involved in B cell self-renewal and proliferation, forming diverse polyclonal B cell repertoire	Osteoporosis	Reduced number of new immature B cells and decreased clonal diversity	(Duy et al., 2010; Miyauchi et al., 2010)
DAP12$^{-/-}$	DAP12: intracellular adaptor protein bearing ITAM	Osteopetrosis	Arrest of B development at pro-preB stage	(Despars et al., 2013)
OPN$^{-/-}$	OPN: involved in cell adhesion, angiogenesis, apoptosis, inflammatory response and tumor metastasis	OC dysfunction; Impaired fracture healing	Reduced Th1 response; increased HSC proliferation	(Nilsson et al., 2005), (Chellaiah et al., 2003)
NF-κB p50$^{-/-}$p52$^{-/-}$	NF-κB: dimer composed of various combinations of p50, p52, p65, c-Rel and RelB; serves as a critical transcription factor and participates in host defense	Osteopetrosis	Impaired B cell development and maturation; defective thymic architecture	(Franzoso et al., 1997)

a) HSCs, hematopoietic stem cells; Tg, transgenic; –/–, knockout; RANK, receptor activator of nuclear factor-kappa B; RANKL, RANK ligand; OPG, osteoprotegerin; TRAF6, tumor necrosis factor receptor-associated factor 6; Bcl-6, B cell lymphoma 6; OPN, osteopontin; mTEC, medullary thymic epithelial cell.

formation of a normal, diverse polyclonal repertoire (Duy et al., 2010). Bcl-6 can also facilitate osteoblastogenesis by recuperating the Runx2 nuclear translocation inhibited by STAT1 and can suppress osteoclastogenesis by attenuating NFATc1 target gene transcription (Fujie et al., 2015; Miyauchi et al., 2010). Bcl-6$^{-/-}$ mice exhibit a distinct OP phenotype, with a markedly reduced new immature B cell pool in the bone marrow and impaired clonal diversity (Duy et al., 2010; Miyauchi et al., 2010). Finally, DNAX-activating protein 12 (DAP12) is a transmembrane immunoreceptor tyrosine-based activation motif (ITAM)-bearing adaptor protein; ITAM signaling is critical in regulating the innate immune response and adaptive immune cell function as well as OC differentiation. DAP12-deficient mice display interrupted immature B cell development at the pro-preB stage and an impaired immune response, along with a distinct osteopetrosis phenotype (Despars et al., 2013; Hamerman et al., 2005).

RANK/RANKL/OPG triad bridges bone remodeling and immune response

RANK/RANKL/OPG signaling in bone remodeling

The receptor activator of nuclear factor-kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) axis is of paramount importance both in physiological bone remodeling and in pathological bone destruction (Theill et al., 2002). This triad is critical in the communication between

the skeletal system and the immune system.

RANKL, RANK and OPG all belong to the tumor necrosis factor (TNF)/TNF receptor (TNFR) superfamily and were discovered during 1996–1997 (Anderson et al., 1997; Lacey et al., 1998; Nakagawa et al., 1998; Wong et al., 1997a; Yasuda et al., 1998). RANKL, also known as TNFSF11, is reported to be expressed by activated T cells, γδT cells, B cells and natural killer cells as well as OBs, osteocytes and fibroblasts (Horwood, 2013). Expression of RANK has been reported in macrophages, dendritic cells (DCs), monocytes and OCs. The interaction of RANKL with RANK not only can enhance DC survival and promote cytokine production and T cell-DC interaction but also can contribute to osteoclastogenesis and OC activation; thus, Rankl knockout ($Rankl^{-/-}$) mice are defective in OC priming and are prone to osteopetrosis (Odgren et al., 2003). People with RANKL gene mutation have been reported to suffer from autosomal recessive osteopetrosis, with function-defective OCs (Sobacchi et al., 2007), whereas transgenic over-expression of RANKL in T cells rescues OC development and restores the bone marrow cavity in $Rankl^{-/-}$ mice, indicating that T cells can regulate bone metabolism through the RANKL pathway (Kim et al., 2000). RANK-RANKL signaling is generally accepted as the key pathway responsible for osteoclastogenesis and inflammation-mediated bone destruction. Although how signal transduction following RANK-RANKL conjugation switches on the bone resorption machinery in OCs remains to be elucidated, certain intermediate processes have been proposed.

Macrophage colony-stimulating factor (M-CSF) plays a critical role in inducing OCs proliferation and survival. And via binding to RANK on OCs with surface RANKL, OBs, osteocytes and activated T cells regulate OCs differentiation and mediate osteoclastogenesis (Xiong et al., 2015). The intracellular domain of RANK contains three cytoplasmic tumor necrosis factor receptor associated factor (TRAF)-binding motifs that can recruit TRAF1, TRAF2, TRAF3, TRAF5, and TRAF6. TRAF6 is particularly essential in mediating RANK-induced nuclear factor-kappa B (NF-κB) activation and inducing NFATc1 expression (Darnay et al., 1999). The role of NF-κB in OCs development and bone resorption has been intensely investigated and reviewed (Abu-Amer, 2013). TRAF6 recruitment sequentially induces the activation of downstream signaling cascades, including NF-κB, c-Fos, extracellular signal-regulated kinase (ERK), c-Src, and c-Jun NH2-terminal kinase (JNK) signaling (Wong et al., 1997b), all of which contribute to NFATc1 activation and amplification. The transcription factor NFATc1 is primed to directly regulate the expression of osteoclastogenic genes, including TRAP, cathepsin K, β integrin and the calcitonin receptor, and then promote the differentiation, proliferation, morphogenesis and activation of OCs (Arron and Choi, 2000; Darnay et al., 1998, 1999; Ikeda et al., 2004; Kobayashi et al., 2001; Wong et al., 1999a).

What's more, co-stimulatory immunoglobulin (Ig) like receptors: OSCAR (osteoclast-associated receptor) and TREM2 (triggering receptor expressed on myeloid cells-2) are associated with ITAM-containing adaptor molecules—Fc receptor common γ unit (FcγR) and DAP12 respectively, and RANK activation leads to the phosphorylation of ITAM and then activate calcium ions signaling which also contributes to NFATc1 priming (Takayanagi, 2009).

The interaction of RANK and RANKL can be impeded by the naturally occurring decoy receptor OPG, which is produced by stromal cells, B lymphocytes and DCs. OPG competes with RANK for RANKL binding with a higher affinity and is capable of blocking signal transduction downstream of RANK and inhibiting OC development and activation. OPG can prevent bone loss and act as a bone protector, as its name implies. OPG-transgenic mice exhibit osteopetrosis and decreased OC numbers, along with extramedullary hematopoiesis (Simonet et al., 1997; Stolina et al., 2007). In contrast, OPG-deficient mice show severe OP and are prone to bone fracture (Bucay et al., 1998; Mizuno et al., 1998). As estrogen promotes OPG production by OBs, OP in postmenopausal women develops partly due to reduced estrogen. The RANK/RANKL/OPG triad is the critical vinculum bridging the immune response and bone metabolism. In particular, activated T cells are capable of inducing morphological maturation and functional activation of OCs and triggering bone absorption through surface RANK. The triad also participates in the cardiovascular, endocrine and nervous systems and plays a critical role in malignant bone metastases, but these topics are outside the focus of this review.

Role of RANK/RANKL/OPG in lymphoid organogenesis and immune response

RANKL was first cloned in T cells and is widely accepted to be important in T/B lymphocyte development and DC survival. The RANK-RANKL interaction can promote CD40 expression, and the ligation of CD40 with CD40 ligand (CD40L), which in turn up-regulates OPG expression on follicular DCs (Yun et al., 1998). Coordinating with other cytokines, RANK/RANKL/OPG orchestrates tuning of the immune response by priming T cell activation, regulating T cell-DC communication, promoting DC survival and participating in lymph node (LN) organogenesis (Anderson et al., 1997; Wong et al., 1997a).

LN organogenesis

Comprehensive expression of RANKL on multiple immune tissues, including the LNs, spleen, thymus and intestinal Peyer's patches, suggests its possible influence on secondary lymphoid organ development and organization.

RANK$^{-/-}$, RANKL$^{-/-}$ and TRAF6$^{-/-}$ mice exhibit completely absent LNs and smaller Peyer's patches but an intact spleen, suggesting a specific and essential role of the RANK/RANKL/OPG triad in LN organogenesis (Dougall et al., 1999; Kong et al., 1999b). It is postulated that RANK-RANKL signaling may act as a growth and survival mediator in the early development of LNs by recruiting lymphopoietic precursors and stimulating the proliferation of stromal cells. When coupled with lymphotoxin (LT)-LTβ receptor (LTβR) signaling, the RANK-RANKL signal forms an important positive feedback loop between lymphoid tissue organizer (LTo) cells, which are of mesenchymal origin, and lymphoid tissue inducer (LTi) cells, which are of hematopoietic origin (Mueller and Hess, 2012). LTi cells express RANK, RANKL and LT. RANK on LTi cells is triggered by interaction with RANKL-bearing LTi cells and leads to enhanced production of LTαβ. Binding of LTαβ with its receptor LTβR on LTo cells in turn induces more RANKL production (Mueller and Hess, 2012; Roozendaal and Mebius, 2011). This self-amplification feedback results in abundant synthesis of chemokines such as CXCL13 and adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1) and mucosal addressin cell adhesion molecule 1 (MAdCAM-1). These molecules help to attract and retain more LTi cells in the LNs and give rise to functional LN establishment (Koning and Mebius, 2012). Moreover, RANK-transgenic mice display hyperplastic LNs, with proliferated vascular and reticular fibroblastic stromal cells (Hess et al., 2012). Thus, RANK-RANKL signaling contributes to the development of LNs by boosting both lymphopoietic and MSC accumulation.

Innate immune response

Mice injected with lipopolysaccharide (LPS) show down-regulated RANKL and up-regulated OPG. RANKL pre-treatment induces macrophage tolerance to bacterial immunization in these mice by suppressing inflammatory cytokine production, protecting the mice from LPS-induced death (Maruyama et al., 2006). For *Tnfsf11*$^{-/-}$ mice, which lack RANKL, LPS stimulation can potentiate increased release of TNF-α and IL-6, and elevated lethality can be observed. Conversely, *Tnfrsf11b*$^{-/-}$ mice, which lack OPG but have a higher serum level of RANKL, exhibit impaired production of IL-6 in response to LPS stimulation (Maruyama et al., 2006). Toll-like receptors (TLRs) have been reported to promote OC formation by up-regulating RANKL expression on fibroblast-like synoviocytes in RA (Kassem et al., 2015; Kim et al., 2007a, 2009). However, TLRs have also been reported to be capable of inhibiting osteoclastogenesis and limiting the pathological bone loss associated with inflammation through inhibition of RANK expression in cooperation with interferon (IFN)- γ (Ji et al., 2009).

Interaction of immune cells and bone cells

Interaction of T cells and bone cells

T cells play a dual role in bone remodeling. Resting T cells potentiate bone protection, probably by inducing OPG production via CD40L costimulation. T cell-depleted mice experience decreased bone density and increased OC numbers (Li et al., 2007). Meanwhile, activated T cells up-regulate surface RANKL expression to enhance OC development and participate in inflammation-associated OP (Kong et al., 1999a). A protective self-induced countermeasure mechanism against activated T cells mediated osteoclastogenesis under physiological conditions has been proposed by Takayanagi et al. (Takayanagi et al., 2000). They discovered that IFN-γ secreted by inflammatory T cells is capable of activating the ubiquitin-proteasome pathway and leading to rapid TRAF6 degradation. This counterbalances enhanced RANKL expression and suppresses OC development. *Ifnr*$^{-/-}$ mice develop accelerated bone destruction compared with wild-type mice when experiencing collagen-induced inflammatory arthritis, which provides further evidence for this protective mechanism. Not all activated T cells are osteoclastogenesis promoters. Th1 and Th2 cells are reported to inhibit osteoclastogenesis by secreting IFN-γ and IL-4, whereas Th17 cells facilitate osteoclastogenesis through their own surface RANKL expression and IL-17-mediated RANKL expression on supporting cells (Sato et al., 2006). By recruiting other inflammatory cells and promoting the release of inflammatory cytokines such as TNF-α and IL-1, Th17 cells polarize the microenvironment in favor of OC development. *Il17*$^{-/-}$ mice of arthritis model and mice with collagen-induced arthritis (CIA) that are injected with a neutralizing antibody against IL-17 are protected from bone destruction (Lubberts et al., 2004; Nakae et al., 2003). In addition, IL-17F released by Th17 cells during bone fracture is a pivotal cytokine in promoting OB maturation and bone healing (Nam et al., 2012). Other cytokines released from T cells during inflammation may be able to interfere with OC formation, e.g., IL-12 alone or in synergy with IL-18 can potently inhibit RANKL-induced OC formation *in vitro*, probably by driving Th1 development and IFN-γ signaling (Horwood et al., 2001).

Although poorly defined and lacking sufficient evidence, T cells may play a role in osteoblastogenesis by coupled up-regulated bone turnover. Rifas et al. deduced that increased alkaline phosphatase activity in bone marrow stromal cells (BMSCs) and elevated mRNA expression of Runx2 and osteocalcin by soluble factors released from T cells indicate the capacity of T cells in inducing OB differentiation (Rifas et al., 2003). Regulatory T cells (Treg) have been shown to be capable of directly affecting bone biology and effectively preventing the local bone destruction and systemic bone loss induced by TNF-α (Zaiss et al., 2010a). Foxp3-transgenic mice are protected from ovariectomy-

induced OP via impaired OC differentiation (Zaiss et al., 2010b), and activated Treg transfer has been reported to improve the clinical outcome in CIA mice and to inhibit OC differentiation both *in vitro* and *in vivo* (Kelchtermans et al., 2009). It is supposed that Treg suppress osteoclastogenesis by cell-cell contact via cytotoxic T-lymphocyte antigen 4 (CTLA4) and by secretion of transforming growth factor (TGF)- β, IL-4 and IL-10 (Kim et al., 2007b; Zaiss et al., 2007). Yet it's worthy of notice that Treg cells possess plasticity and pathogenic Th17 cells could originate from Treg. Those IL-17$^+$Foxp3$^+$T cells are found accumulating in the synovium of inflamed joints of patients with RA and are thought as potent osteoclastogenic and arthritogenic T cells expressing RANKL. Contrary to the anti-inflammatory effect of classic Treg, IL-17$^+$Foxp3$^+$T cells are "inflammatory Treg" which may be the product of imbalanced cytokines status and intense contest between autoimmunity and self-tolerance (Komatsu et al., 2014). Anyway, anti-TNF-α therapy can restore Treg function via increased Foxp3 phosphorylation and adjust the balance between Treg and Th17 cells (Nie et al., 2013), to which its effectiveness in RA can be partly owing. Modulating Treg development and increasing Treg numbers may therefore be a promising therapeutic strategy in diseases associated with over-activated OCs and accelerated bone loss.

The RANK/RANKL/OPG triad is of great importance in T cell development. T cell negative selection and Foxp3$^+$ Treg emergence in the thymus are dependent on the medullary thymic epithelial cell (mTEC) compartment and the thymic medullary microenvironment (Aschenbrenner et al., 2007; Hikosaka et al., 2008; Ohigashi et al., 2011). mTECs present self-antigens, participate in establishing T cell central tolerance checkpoints and contribute to autoreactive T cell clonal deletion in the thymus. RANK, OPG, CD40, and LTβR expressed on mTECs cooperate to promote mTEC development and help to establish and maintain the homeostasis of the thymic medullary microenvironment (Akiyama et al., 2008). *Rankl*$^{-/-}$ mice exhibit blocked differentiation from CD25$^+$CD44$^-$ to CD25$^-$CD44$^-$ thymocytes and reduced thymic cellularity (Kong et al., 1999b). Similar progression defects can also be observed in OPG-transgenic mice and recombinant-OPG-treated mice (Stolina et al., 2007).Th1 cytokines produced by *rankl*$^{-/-}$ T cells are significantly reduced under stimulation with anti-CD3/anti-CD28 and cannot be restored by exogenous RANKL (Kong et al., 1999b). In contrast, RANKL-transgenic mice display increased mTEC numbers and an enlarged thymic medulla, indicating the regulatory function of the RANK-RANK-OPG signal in the early development of T cells. RANKL signaling in the thymus influences the intrathymic Treg pool by enhancing peripheral Treg recirculation back to the thymus (McCarthy et al., 2015). OCs have been reported to be capable of inducing γδT cell activation and proliferation as well as supporting γδT cell survival *in vitro*, mainly through a TNF-α-mediated pathway or direct cell-cell contact (Pappalardo and Thompson, 2015). Conversely, activated γδT cells negatively regulate OC formation by secreting IFN-γ (Pappalardo and Thompson, 2013).

Interaction of B cells and bone cells

The B cell lineage has a profound reciprocal interaction with the bone system (Manilay and Zouali, 2014). B cell-produced OPG has been proven to be an important regulator in bone metabolism (Li et al., 2007), and this production can be augmented by T cells via CD40-CD40L costimulation (Yun et al., 1998). B cell depletion in mice leads to significantly decreased OPG and increased bone resorption, which can be rescued by B cell reconstitution. This finding is of certain physiopathological importance in protecting bone against damage when confronted with infection and inflammation. Meanwhile, B cells are also a source of RANKL, thus playing a role in shaping OC development. Under certain pathological conditions, RANKL produced by B cells may neutralize or overwhelm B cell-derived OPG, resulting in accelerated bone loss. *In vitro*, activated B cells can promote the development and maturation of OCs by producing multiple cytokines (Choi et al., 2001). The IgG immune complex (IgG-IC) comprehensively regulates the immune response through FcγR signaling, but meanwhile is also a potent stimulator of OC formation. High titers of IgG in CIA mice strongly promote osteoclastogenesis, which can be abrogated by depleting IgG in the serum. Negishi-Koga et al. have recently reported that the engagement of FcγRs provides costimulatory signals for osteoclastogenesis (Negishi-Koga et al., 2015). IgG-IC-FcγR signaling participates in OC expansion and bone homeostasis breakdown. FcγRIIB and FcγRIII are negative modulators of osteoclastogenesis, with a mechanism of competitive occupation, depleting the availability of FcγR to other activating ligands. Temporary down-regulation of FcγRIII is a necessary physiological process during OC differentiation (Negishi-Koga et al., 2015). Harre et al. further verified that desialylated IgG-ICs with enhanced binding and engagement of FcγRs could be more favorable for driving osteoclastogenesis (Harre et al., 2015).

B cell commitment and maturation are dependent on cell-cell contact with OBs (Zhu et al., 2007), while OCs can support the survival of plasma cells independent of B lymphocyte stimulation through cell-cell contact (Geffroy-Luseau et al., 2008). Absence of preB and proB cells in Col2.3Δ-TK-transgenic mice after selective depletion of OBs confirmed the role of OBs in B cell lymphopoiesis (Zhu et al., 2007). OB-derived RANKL is essential for preB cells to develop into mature B cells, and pre-B cells exhibit arrested development in *rankl*$^{-/-}$ mice (Zhu et al., 2007). But the role of the RANK-RANKL axis in B cell physiology is far more sophisticated and still a matter of debate. Recently, *rankl*$^{-/-}$ mice are found to exhibit relative expansion of

marginal zone B cells and plasma cells, increased Ig secretion and spontaneous germinal center formation, which may be attributed to increased regulatory B cell numbers and enhanced IL-10 production (Marrella et al., 2015). Both OBs and multipotent stromal cells are the main sources of stromal cell-derived factor 1 (SDF-1), IL-7 and CXCL12, which collaborate to construct indispensable niches for B cell development (Woodward, 2010; Wu et al., 2008; Zhu et al., 2007). $OPG^{-/-}$ mice have been reported to have accumulated transitional B cells in the spleen, enhanced B cell proliferation under IL-7 stimulation, and compromised Ig switching in response to T cell-dependent antigen (Yun et al., 2001). Paradoxically, OPG-transgenic mice exhibit no significant functional alterations in humoral immune responses (Stolina et al., 2007). However, elimination of functional RANKL or RANK reveals dramatically defective B cell development and hypogammaglobulinemia both in mice and in humans, which may mainly be due to osteopetrosis and a shrinking bone marrow cavity (Guerrini et al., 2008; Kong et al., 1999b).

Interaction of DCs and bone cells

DCs are highly differentiated antigen-presenting cells with the plasticity to transdifferentiate into OCs under appropriate stimulation (e.g., in the presence of M-CSF and RANKL) (Alnaeeli et al., 2006; Rivollier et al., 2004). RANKL is capable of protecting DCs from Fas ligand-induced apoptosis (Chen et al., 2004). The synergy of RANKL and CD40L, which are both expressed by activated T cells, controls DC survival and stimulates proinflammatory cytokine production by DCs (Josien et al., 1999, 2000). Similar features can be observed in $OPG^{-/-}$ mice (Chino et al., 2009; Wong et al., 1999b). RA provides a microenvironment in the synovium and synovial fluid that is abundant in pro-inflammatory cytokines capable of supporting transdifferentiation. DC-derived OCs have been suggested to be involved in osteolytic lesions (Santiago-Schwarz et al., 2001). DCs can also act as OB precursors, and T cell-DC interaction may directly contribute (Alnaeeli et al., 2006) to osteoclastogenesis in a RANKL-dependent manner (Page and Miossec, 2005). Considering the important role of DCs in immune response initiation and perpetuation as well as their status as efficient inducers of Th17 cells (Dhodapkar et al., 2008), DCs are important mediators of inflammation-associated bone loss and provide a promising therapeutic target for modulating inflammatory bone destruction (Alnaeeli et al., 2007).

Role of cytokines in bone homeostasis

Multiple cytokines and factors are involved in the complex bone homeostasis regulatory network, especially during rheumatic bone erosion, which has been reviewed in literature (Arboleya and Castaneda, 2013) and is also summarized in Table 2.

M-CSF

M-CSF is a critical growth stimulator for the macrophage lineage and OC progenitors. In the spontaneous-mutant osteopetrotic mouse strain *op/op,* decreased OC numbers coupled with impaired bone resorption and defective M-CSF production are key characteristics (Felix et al., 1990b). *Op/op* mice are specifically deficient in M-CSF and exhibit osteopetrosis. Replenishment with recombinant M-CSF can induce OC formation and restore the bone marrow cavity that is absent in *op/op* mice (Felix et al., 1990a). M-CSF stimulates RANK expression in OC precursors, promotes OC differentiation and prolongs OC survival *in vivo* (Fuller et al., 1993) and is indispensable for inducing OC formation from monocytes/macrophages *in vitro* (Marino et al., 2014).

TNF-α

TNF-α can enhance RANKL expression on OBs and M-CSF production by stromal cells, can augment the responsiveness of OC precursors to RANKL and can stimulate OC maturation. Moreover, TNF-α can induce the expression of OSCAR, which in turn costimulates OC formation. By modulating Wnt signaling activation, inhibiting the expression of the transcription factor Runx2 and up-regulating the RANKL/OPG ratio, TNF-α suppresses OB differentiation while promoting OC maturation. In the presence of M-CSF, TNF-α coupling with IL-1 can induce mouse bone marrow macrophages to develop into $TRAR^{+}$ OCs (Yamashita et al., 2015; Zhang et al., 2001). Flourishing clinical application of TNF-α blockers in RA and other types of inflammatory arthritis has yielded inspiring therapeutic effects in preventing progressive bone destruction, even reversing bone erosion.

IL-1

IL-1 is another potent osteoclastogenesis inducer produced by macrophages, MSC and lymphocytes. IL-1 is capable of up-regulating RANKL expression on BMSCs and inducing OC precursors to differentiate into mature OCs as well as prolonging OC survival and enhancing OC bone-absorbing activity. TNF-α can induce IL-1 production, coordinate with IL-1 and depend on IL-1 to mediate OC activation and promote inflammation-associated bone loss (Wei et al., 2005). Bone loss induced by estrogen deficiency occurs partly via IL-1, and blockade of IL-1 can prevent bone loss both in postmenopausal women and in ovariectomized mice.

IFN-γ

IFN-γ abrogates the signaling transduction downstream of RANKL and rescues OP in ovariectomized mice (Duque et al., 2011; Takayanagi et al., 2000). IFN-γ also plays a role in osteoblastogenesis by promoting the differentiation of MSC into OBs (Duque et al., 2009). And by mediating

Table 2 Cytokines involved in bone remodeling and the immune response[a)]

Cytokine	Source	Effect on OBs/OCs	Effect on immunity
TNF-α	Th1, macrophage, DC	OB formation ↓ / ↑ ; OC formation ↑ ;	Pro-inflammation
IFN-γ	Th1, natural killer cell	OB formation ↑ ; OC formation ↓ / ↑ (depends on context)	Cellular immunity
IL-12	Macrophage, DC	OC formation ↓	Th1 cell differentiation; IFN-γ and GM-CSF induction
IL-18	Macrophage, DC	OC formation ↓	Th1 cell differentiation, IFN-γ induction
GM-CSF	Th1	OC formation ↓	Macrophage recruitment; pro-inflammation
IL-4	Th2	OC formation ↓	Humoral immunity
IL-6	Macrophage, DC, Th2 synovial fibroblast	OC formation ↑	Pro-inflammation; Th17 induction
IL-10	Th2, Treg	OC formation ↓	Anti-inflammation
IL-17	Th17, γδT	OB formation ↓ ; OC formation ↑	Pro-inflammation
IL-23	Macrophage, DC	OC formation ↑	Th17 induction
IL-1	Macrophage, DC	OC formation ↑	Pro-inflammation
TGF-β	Treg, OB, BMSC	OC apoptosis ↑	Anti-inflammation, involved in Th17/Treg differentiation
OSM	OB, OC, macrophage, T cell	OB formation and mineralization ↑ ; OC formation ↑ (pathological condition)	Induction of megakaryocyte hematopoiesis
IL-7	BMSC	OC formation ↑	Promotion of T/B cell development
IL-27	Macrophage, DC	OC formation ↓	Th1 and Treg ↑ ; Th17 induction

a) DCs, dendritic cells; OSM, oncostatin M. Treg, regulatory T cell; Th17, IL-17 secreting T cell; BMSC, bone marrow stromal cell

rapid TRAF6 degradation via activating ubiquitin-proteasome, IFN-γ suppresses OC development and acting as a bone-protective factor. But IFN-γ can also act as a pro-absorptive cytokine by stimulating antigen-dependent T activation and promoting T cell secretion of TNF-α and RANKL (Gao et al., 2007). Therefore, the paradoxical role of IFN-γ in bone remodeling involves directly targeting OC precursors to inhibit osteoclastogenesis and indirectly stimulating OC formation to facilitate osteoclastogenesis. The influence of IFN-γ on bone homeostasis is dependent on the net effects in different contexts.

IL-4

IL-4 is a pleiotropic cytokine that has also been found to be a potent negative regulator of OC formation and OC activation through inhibiting NFATc1 and c-Fos expression, inducing OPG production and attenuating RANKL and RANK expression via a mechanism depending on STAT6-mediated NF-κB signaling inhibition (Abu-Amer, 2001; Moreno et al., 2003; Palmqvist et al., 2006; Yamada et al., 2007).

IL-10

In bone remodeling, synthesis of bone proteins (e.g., alkaline phosphatase, collagen and osteocalcin) and mineralization of extracellular matrix can be suppressed by IL-10. Additionally, by inhibiting the intranuclear translocation of NFATc1, IL-10 can prevent RANKL-mediated osteoclastogenesis at an early stage (Evans and Fox, 2007; Mohamed et al., 2007). IL-$10^{-/-}$ mice thus develop an osteopenic phenotype with increased bone fragility (Dresner-Pollak et al., 2004).

IL-6

IL-6, produced by macrophages, DCs and BMSCs, is a potent stimulator of OC activation and bone absorption via RANKL up-regulation. In synergy with TNF-α, IL-6 plays a pivotal role in the synovitis with pannus formation and contributes to the pathogenesis of RA. Blockade of IL-6 ameliorates the osteoclastogenesis induced by active RA sera *in vitro* (Pathak et al., 2014) and suppresses joint destruction in FcγRIIB-deficient RA mice (Ohtsuji et al., 2015).

IL-17

Th17 cells are IL-17-secreting cells with robust RANKL expression and vigorous pro-inflammatory potency (Takayanagi, 2009). IL-17 has been shown to synergistically induce RANK expression on OC precursors and promote RANKL expression on OBs, BMSCs and synovial fibroblasts, thus supporting OC development (Adamopoulos and Bowman, 2008; Adamopoulos et al., 2010). IL-17 is also thought to play a critical role in progressive periodontitis (PD) and erosive arthritis. Neutralizing IL-17 in CIA mice therefore helps to reduce joint inflammation, cartilage destruction and bone erosion.

TGF-β

TGF-β positively modulates bone formation by inducing OB precursor differentiation and migration and abrogating OB apoptosis, possibly by enhancing Runx2 expression (Lee et al., 2000). However, in the later stage of OB maturation, TGF-β1 inhibits the proliferation and mineralization of OBs in accordance with Runx2 suppression (Alliston et al., 2001; Kang et al., 2005).

Oncostatin M (OSM)

OSM is a pleiotropic cytokine belonging to the IL-6 family that influences both bone formation and bone resorption. Irrespective of its role in malignancy, OSM, produced by cells of hematopoietic origin (e.g., T lymphocytes and macrophages) and mesenchymal origin (e.g., OBs and osteocytes) in the bone marrow microenvironment, can control both OB and OC formation. In particular, OSM promotes OB differentiation and directs stromal cells to OB commitment. OSM is also capable of inducing RANKL expression on OBs to drive osteoclastogenesis and has the potential to contribute to bone destruction in inflammatory arthritis and bone metastasis in combination with IL-1 and TNF-α (Bolin et al., 2012; Hui et al., 2005; Le Goff et al., 2014). Therefore, OSM exerts both anabolic and catabolic effects on bones and participates in pathological bone destruction and new periosteal bone formation.

OPN

OPN is a cytokine with pleiotropic properties that is synthesized by multiple cell types, including immune cells such as DCs and T/B lymphocytes and bone cells such as OBs. OPN plays a role in bone remodeling, modulates mineralization of the skeleton and participates in absorption of mineralized bone by anchoring OCs onto the bone surface and stimulating interaction of OCs and stromal cells (Denhardt et al., 2001; Heinegard et al., 1995). OPN is also involved in regulating the immune response to injury; infection; and auto-inflammatory disease, such as RA, via integrins and CD44 (Xu et al., 2005). Although not indispensable, OPN modulates cell-mediated responses by promoting the Th1 response, as indicated by an abrogated Th1 response in $OPN^{-/-}$ mice, and is also capable of supporting Th17 and B cell differentiation (Rittling and Singh, 2015) as well as influencing IFN-γ, IL-10 and IL-12 production (Ashkar et al., 2000).

Complement

The complement system serves as an important component of innate immunity by opsonizing antigens, mediating phagocytosis, modulating cell migration and apoptosis, inducing cytokine release and promoting the inflammatory reaction, thus playing a critical role in defense against invasive microorganisms and in clearance of cellular debris of self-origin (Zipfel and Skerka, 2009). Evidence shows that the complement system also plays a role in bone biology. For example, modulation of complement C3a and C5a have been reported to modulate OB formation and OC activation (Ignatius et al., 2011), and reduction of C3aR/C5aR activity inhibits OC generation (Tu et al., 2010). In addition, OC-derived C3a stimulates OB differentiation (Matsuoka et al., 2014). In synergy with IL-1β, under pro-inflammatory conditions, C3a and C5a are capable of inducing IL-6 and IL-8 release from OBs and up-regulating RANKL/OPG expression, culminating in the inflammatory phenotype of OBs (Ignatius et al., 2011), which represents bidirectional communication between OCs and OBs.

CLINICAL DISEASES ASSOCIATED WITH OSTEOIMMUNOLOGY

RA (rheumatoid arthritis)

RA is a typical disorder for demonstrating the connotations of osteoimmunology. Specifically, RA is an autoimmune-mediated chronic inflammatory arthritis with high morbidity and a high rate of crippling. Synovial pannus, juxta-articular osteopenia, and erosion of the cartilage and subchondral bone are the pathological characteristics of RA. Increased levels of activated OCs are the predominant disturbance of bone homeostasis that occurs, and exaggerated levels of pro-inflammatory cytokines, including IL-1, TNF and IL-6, are remarkable both in affected joints and in the peripheral serum (Le Goff et al., 2013). Augmented RANKL expression in RA synovium by synovial fibroblasts and activated T cells has also been found (Gravallese et al., 2000). It has been confirmed that synovial fluid mononuclear cells in flamed joints have the potential to spontaneously develop into functional OCs *ex vivo*, which is further augmented in the presence of RANKL and M-CSF (Greisen et al., 2015). Bone loss and erosion in RA are mainly attributed to enhanced RANKL expression on activated synovial fibroblasts; infiltrative mononuclear cells; and activated T cells, and especially Th17 cells from RA tissue. The concentration of soluble RANKL, which is probably derived from T cells, is comparatively higher than that of OPG in the synovial fluid in RA patients (Kotake et al., 2001). RANKL-loaded activated T cells can directly trigger osteoclastogenesis, leading to OC amplification and bone loss. However, this pro-osteoclastogenic effect may be partly counterbalanced by IFN-γ secreted by activated T cells themselves. Peripheral blood monocytes and synovial macrophages have the potentiality of differentiating into OCs in certain microenvironments (e.g., in the presence of M-CSF and 1,25(OH)2 vitamin D3) (Fujikawa et al., 1996a, b; Takayanagi et al., 1997), which may serve as a critical mechanism of bone destruction in RA. In a mouse model, OPG treatment at disease onset could abolish bone matrix degeneration, inhibit OCs accumulation and prevent cartilage destruction and joint crippling (Kong et al., 1999a).

The crucial role of cytokines central to the pathogenesis of RA has been reviewed in detail in the literature (McInnes and Schett, 2007).

Anti-citrullinated peptide antibody (ACPA) is a disease-specific antibody with potent pathogenicity for RA via its pro-osteoclastogenic effect. During OC differentiation, specific N-terminal vimentin citrullination is induced. ACPAs can bind to the OC surface, leading to TNF-α release from OC precursors and stimulating robust osteoclastogenesis and bone absorptive activity (Harre et al., 2012). High titers of ACPAs are strongly associated with early onset and rapid progression of bone lesions. As mentioned before, the pro-osteoclastogenic potency of IgG-ICs is greatly determined by their sialylation levels, in that higher sialylation of the IgG-Fc glycon inhibits OC activation. ACPAs are found to be sialylated at a much lower level than random IgG, which is in accordance with the potency of ACPAs in bone damage. Artificially enhancing the sialylation levels of ACPA *in vitro* abolishes its activity in driving OC maturation, which may act as a new strategy to treat human RA in the future. In fact, experiments in a CIA mouse model treated with ManNAc, a sialic acid precursor capable of increasing protein sialylation levels, has displayed promising efficacy (Harre et al., 2015). Activated B cells in RA not only produce antibodies (e.g., ACPAs) and secrete inflammatory cytokines but also express RANKL, all of which favor OC differentiation. Thus, the bone-protective efficacy of rituximab by depletion of B cells can be explained and expected (Dohn et al., 2009).

The concept of osteoimmunology strengthens our understanding of the biologic agents that have now been widely used in RA therapy and provides potential targets for new strategies. Except for B cell depletion, cytokine inhibition, including via TNF inhibitors (etanercept, infliximab, adalimumab and golimumab) and IL-6 receptor blockade (tocilizumab), has been confirmed to be clinically effective in retarding the progression of the bone erosion process. CTLA4 switches off the costimulatory CD28:CD80/86 interaction and provides a negative regulatory signal for OC differentiation (Axmann et al., 2008). CTLA4-Ig (abatacept) introduction into the therapy for active RA has also been proven to be effective (Schiff, 2011), and the mechanism is multifaceted, beyond T cell costimulation and activation (Cutolo et al., 2016) (Figure 2).

OP (osteoporosis)

Postmenopausal OP and glucocorticoid (GC)-induced OP (GIOP) are the main types of OP that rheumatologists usually encounter in routine practice. Decreased estrogen in the circulation after menopause will lead to OP, with bone resorption outpacing bone formation. GCs are the indispensable cornerstone of the management of autoimmune disease,

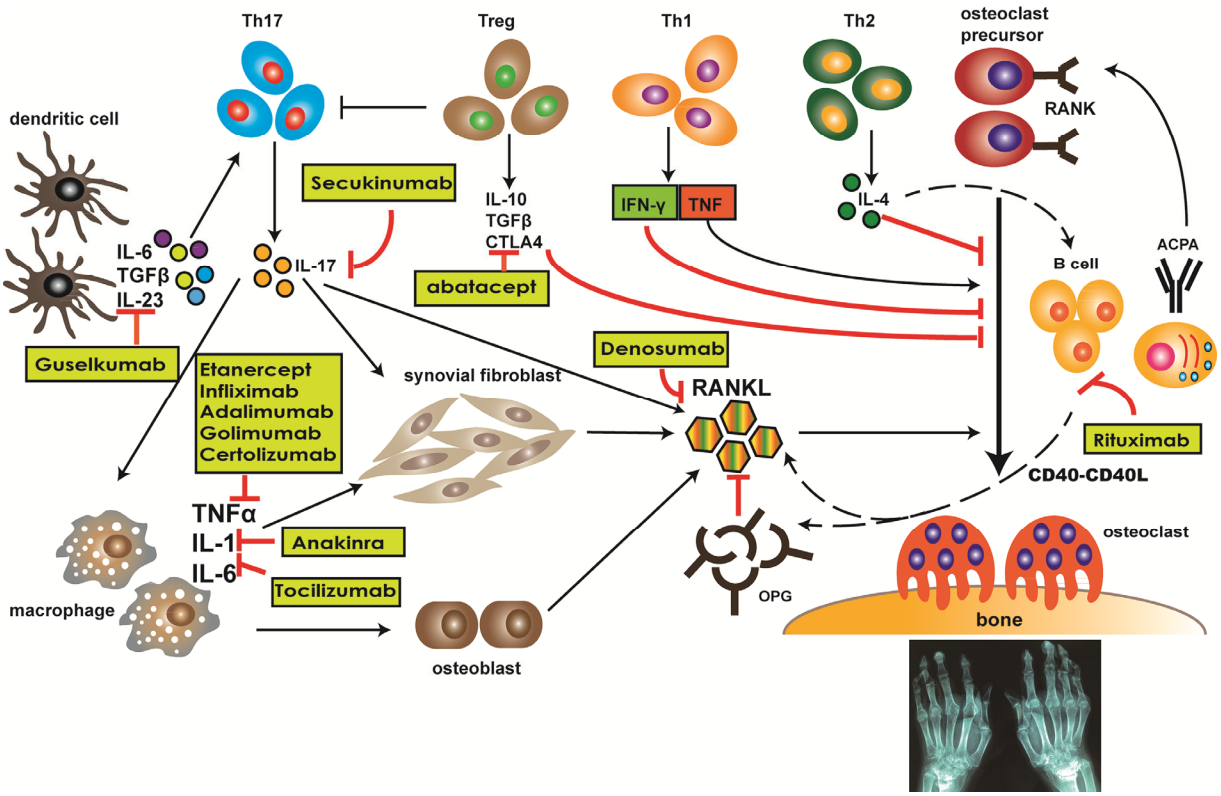

Figure 2 Components of osteoimmunology contribute to bone absorption in RA and target therapy. Immune cells interact with bone cells via cytokines and surface molecules to mediate bone erosion and inflammation-associated bone loss in RA. TNF-α, IL-6 and IL-1 are the most important pro-inflammatory cytokines in this context, and RANKL is the primary signal in OC differentiation. These recommended therapeutic targets have been confirmed in clinical practice or are waiting for validation in clinical trials.

with potent suppressive effects on inflammation, but GC exposure is widely known for its adverse effects on bone remodeling, leading to a high risk of vertebral fracture and femur head necrosis. In particular, GCs inhibit bone formation and promote bone resorption to accelerate bone loss, probably by prolonging the survival of OCs and inducing apoptosis of OBs and osteocytes (Mitra, 2011). Further research indicates that GCs can inhibit the Wnt pathway, which is pivotal in OB differentiation, survival and function.

New strategies to improve bone turnover and strengthen bone protection have been employed in OP. Denosumab, which is an antibody against RANKL, is effective in increasing bone mineral density and reducing the bone fracture risk in patients with OP and has been approved for postmenopausal OP treatment. Estrogen and estrogen receptor modulators are also effective in preventing bone loss in postmenopausal women, but adverse effects should be evaluated and monitored. Odanacatib, an inhibitor of cathepsin K, exhibits similar bone protection effects, and approval can be expected soon. Other agents, such as a PTH-related peptide (PTHrp) analog and a Src tyrosine kinase inhibitor, are at the stage of clinical or preclinical evaluations (Makras et al., 2015; Suresh and Abrahamsen, 2015).

SPA (spondyloarthropathy)

Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are representative SPA disorders with distinctive osteoclastogenic features. Syndesmophytes and enthesophytes, vertebral bone loss and sacroiliac joint erosion with or without peripheral joint destruction coexist in SPA, indicating disturbed bone remodeling. Enhanced Th17 cell numbers and IL-17 serum levels have also been observed and are believed to be involved in the pathogenesis (Mei et al., 2011; Raychaudhuri et al., 2015; Shen et al., 2009). IL-22 produced by Th17 cells exerts anabolic effects on bone remodeling by stimulating Wnt and BMP signaling and enhancing bone formation (Goldring, 2013). Dickkopf-1 (DKK-1) is a natural inhibitor of Wnt signaling that can induce OPG production and that is devoted to osteoblastogenesis. In contrast to increased DKK-1 in RA, serum DKK-1 in AS has been reported to be decreased and to be inversely correlated with AS disease severity (Yucong et al., 2014). Blockade of DKK-1 in mice induces ankylosis of sacroiliac joints (Uderhardt et al., 2010), indicating that manipulating Wnt signaling may be a promising therapeutic strategy to prevent osteophyte formation at the inflammation site (Schett et al., 2008).

PD (periodontal disease)

PD is a chronic disease associated with alveolar bone loss and gingival tissue inflammation. Its etiology is an immune reaction to oral bacteria, and especially *Porphyromonas gingivalis (P. gingivalis).* The compromised periodontium will lose its supportive function, and the affected teeth will ultimately fall out. PD and RA are closely correlated with a high comorbidity and parallel severity (de Pablo et al., 2008; Mercado et al., 2003). Both diseases have common risk factors, such as shared HLA-DRB1 epitope alleles and smoking. *P. gingivalis* is thought to be the major, although not exclusive, cause of PD. The pathogen specifically contributes to protein citrullination, which subsequently stimulates the host immune response and induces autoantigen production, acting as a trigger in the pathological reaction of RA (Lundberg et al., 2010). It has been reported that antibodies to *P. gingivalis* are more commonly observed in RA patients and are significantly correlated with anti-cyclic citrullinated peptide (CCP) titers in RA patients, revealing the inherent connections between the two diseases (Mikuls et al., 2009). What's more, a considerable proportion of Treg-derived IL-17 producing cells (IL-17$^+$Foxp3$^+$ T cells) have been found in PD lesions indicating the conversion from Treg to Th17 may play a role in the pathogenesis of PD (Okui et al., 2012).

Periodontal bone loss is associated with increased infiltration of B cells and T cells with enhanced RANKL expression and is capable of inducing OC maturation in a RANKL-dependent manner (Kawai et al., 2006). Recently, Li et al. have found that silencing the Atp6v1c1 gene locally can reduce OC numbers and reverse bone destruction in PD as well as inhibiting DC and macrophage infiltration and down-regulating pro-inflammatory cytokine production (Li et al., 2015). Atp6v1c1 is expressed by OCs and localized on the ruffled border, and it is responsible for encoding a proton pump subunit that is required for OC-mediated extracellular acidification. The acidic milieu is required for solubilization of calcium from bone (Li et al., 1999).

FUTURE PERSPECTIVES

Advances in osteoimmunology expand and deepen our understanding of the underlying pathophysiological mechanisms in certain osteoarticular disorders and systemic inflammatory diseases. Although the precise mechanisms underlying the intimate communication and regulation involved remain to be elucidated, promising strategies have been developed based on current and growing knowledge in this field. Thinking of the skeletal system and immune system as an integrated unit is paving the way to preventing bone loss and bone destruction, which affect enormous populations. As an osteoclastogenesis inducer, RANKL is theoretically a promising target in osteopenic disease. Denosumab, a human IgG2 monoclonal antibody against RANKL, has been approved to treat postmenopausal OP and bone metastases. A preliminary clinical trial has shown that Denosumab has certain effects in reducing the progression of RA (Cohen et al., 2008). Along with growing understanding of the pathological mechanisms of RA and the

wide use of TNF-blocking biologics with inspiring effects, knowledge of osteoimmunology is rapidly growing and expanding, and new strategies are emerging.

CONCLUSIONS

The skeletal system and immune system are closely correlated, and growing knowledge of their interaction and interdependence has given birth to the new interdisciplinary field of osteoimmunology. The RANK/RANKL/OPG triad acts as the central regulator of the crosstalk between the two systems. This triad is not only the pivotal mediator of osteoclastogenesis, leading to bone loss, but also an indispensable factor for LN organogenesis and B cell maturation, in addition to providing potent survival signals for DCs to initiate immune responses. Design of therapeutic approaches should consider these bidirectional effects. Manipulation of the OPG signal or intervention in RANKL expression and the expression of other signaling molecules involved may be promising to ameliorate osteopenic problems in multiple clinical disorders, regardless of their origin.

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